## REMARKS

**Pending Claims**

Claims 1-7 are pending in the application. No claims are amended.

**Discussion of Rejection of Claims 1-2 and 4-6 under 35 U.S.C. § 103(a)**

Claims 1-2 and 4-6 are rejected under 35 U.S.C. §103(a) as obvious in light of U.S. Patent No. 5,437,982 to Catterall et al. ("Catterall") in view of Connolly et al., Biosensors and Bioelectronics, 1990 5: 223-234 ("Connolly") and U.S. Patent No. 5,981,268 to Kovacs et al. ("Kovacs"). Applicant respectfully traverses. To establish a *prima facie* case of obviousness, the Examiner must establish at least three elements. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02*. And finally, the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007).

Amended Claim 1 recites, among other things, a "method of screening a plurality of drug candidate compounds against a target ion channel comprising expressing said target ion channel in a population of host cells; placing a plurality of said host cells into each of a plurality of sample wells; adding a candidate drug compound to at least one of said plurality of sample wells;

providing extracellular electrodes extending down into said at least one well; affecting the target ion channel by modulating a transmembrane potential of said host cells in said at least one well with an application of a series of electric field pulses applied with said extracellular electrodes so as to set said transmembrane potential to a level suitable for a specific ion channel activation state or transition between states, wherein the frequency of the electric field pulses (*f*) is within the range $\tau_M^{-1} \leq f \leq \tau_b^{-1}$ where $\tau_M$ is a time constant for decay of transmembrane potential changes, and $\tau_b$ is an average target ion channel open time, and wherein the pulses at said frequency cause a sustained transmembrane potential change via a stepwise accumulation or loss of ions over the course of said series of pulses; and detecting transmembrane potential characteristics of said plurality of cells over an area of observation in said at least one well to detect an effect of said candidate drug compound on said target ion channel."

Applicant previously presented evidence that those of skill in the art did not consider using extracellular electrodes as claimed to be obvious. Among that evidence was the article "Characterization of voltage-gated sodium-channel blockers by electrical stimulation and fluorescence detection of membrane potential" Nature Biotechnology, Volume 24, Number 4, April 2006 and U.S. Patent No. 7,276,206 to Augustine et al. Both the publication of the Nature Biotechnology article and the later filed Augustine patent application support the Applicant's assertions that those of skill in the art at the time the invention was made would not find it obvious to manipulate transmembrane potential as claimed with extracellular electrodes.

In the latest Office Action, the Examiner states that Kovacs "provides evidence contrary to the teachings of the post-filing date art pointed out by the applicant. Kovacs demonstrates that the use of extracellular electrodes to apply energy to cells and to activate a voltage-gated ion channel was known at the time the invention was made." *Office Action of 13 November 2009* at page 9.

However, the language of Claim 1 is not the same as the Examiner's characterization. As highlighted above, the claim requires that the pulses at said frequency cause a sustained transmembrane potential change via a stepwise accumulation or loss of ions over the course of said series of pulses; and detecting transmembrane potential characteristics of said plurality of cells. Kovacs teaches culturing cells onto a microfabricated array of electrodes. When an electrical signal is applied between a microelectrode and a large reference electrode, a current is

detected. There is no teaching in Kovacs, however, of the above claimed sustained transmembrane potential changes. Kovacs detects a current through the cell. Thus, in Kovacs, charge enters one portion of the cell and exits another. Although this current may be dependent on the opening of ion channels, there is no indication that any transmembrane potential change is occurring. Kovacs does not teach setting a transmembrane potential to any specific level, nor is there any reason to suspect that charge is accumulating in the cells of Kovacs.

To help demonstrate this point, attached as Annex 1 is some experimental data generated by the applicants where the stimulus waveform of Kovacs is used with extracellular electrodes in wells of a multi-well plate as described in the present application. At column 16, line 6, a 100 mV peak to peak sinusoidal stimulus is described in Kovacs. In Annex 1, it can be seen that no significant transmembrane potential change is seen with such a waveform until near or above 10 V, which is the absolute maximum voltage contemplated (but never used) by Kovacs (see column 16, lines 16-17 of Kovacs). As discussed in the interview, there is no indication that results similar to Figure 14 of the present application, with sustained transmembrane potential changes produced by ion accumulation or loss in the cell is produced with the system and method described by Kovacs.

As discussed previously, the combination of Catterall and Connolly also does not teach these limitations of Claim 1. The Examiner asserts Connolly teaches or suggests that extracellular electrodes are a suitable substitute for an intracellular patch clamp. *Office Action of 13 November 2009* at page 5; *Office Action of 17 November 2008* at page 4. This assertion is not accurate. Merely because extracellular electrodes can initiate beating of cardiac cells does not mean they are "suitable substitutes" for a patch clamp. Evidence of this can be found in Figures 10 and 14 of the present application, which illustrate examples of the sustained changes made possible with the claimed method. These changes are qualitatively different from the beating produced by Connolly.

Thus, for at least the reasons explained above, the limitations recited in Claim 1 would not have been obvious in light of Catterall, Connolly and Kovacs. Thus, Applicant respectfully requests the Examiner's rejection be reconsidered and withdrawn.

**Discussion of Rejection of Claims 1-7 under 35 U.S.C. § 103(a)**

Claims 1-7 are rejected under 35 U.S.C. §103(a) as obvious in light of U.S. Patent No. Catterall in view of Connolly, Kovacs and either Tung et al. (Biophysical Journal) or Tsien et al (WP 96/41166) or Denyer et al (Drug Discovery), all of record. Applicant respectfully traverses these rejections. Claims 2-7 each ultimately depend from, and thus contain all limitations of, amended Claim 1. As discussed above with regard to the combination of Catterall, Connolly and Kovacs, all elements of Claim 1 are not taught by these references. Tung, Tsien and Denyer do not remedy the deficiencies of Catterall, Connolly and Kovacs with respect to Claim 1. Indeed, the Examiner does not assert such, only citing Tung, Tsien and Denyer as teaching repetitive application of biphasic field pulses and/or drug screening techniques. Because the cited art, alone or in combination, does not teach all features of Claim 1, Claim 1 and the claims dependent therefrom are not rendered obvious by these references. At least for this reason, Applicant respectfully requests the Examiner's rejections be reconsidered and withdrawn.

**No Disclaimers or Disavowals**

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

## CONCLUSION

Applicant has endeavored to address all of the Examiner's concerns as expressed in the previous Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of these amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested. If any issues remain that could be resolved by telephone, the Examiner is invited to call the undersigned directly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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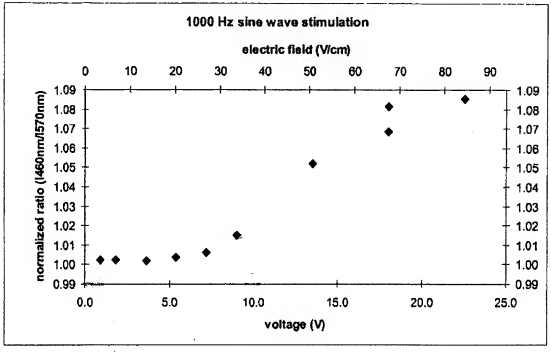
## ANNEX 1 – EXPERIMENTAL DATA




Stimulation voltage and field strength versus membrane-potential response. Normalized peak ratio responses are plotted as a function of both voltage at the electrodes (bottom x-axis) and electrical field strength between the electrodes (top x-axis).

The peak response was taken from a period from 0.1 to 1 second from the beginning of stimulation. Stimulation voltages between the electrodes ranged from 0.9 Volts to 22.5 volts at a frequency of 1000 Hz for 3 seconds.

HEK293 cells expressing a voltage gated sodium channel were loaded with voltage sensitive dyes as described in Huang *et al.* Other methods used were the same as in Huang *et al.* except that a 384 well plate was used rather than a 96 well plate and fluorescence emission was detected with camera at 20 Hz rather than a photomultiplier at 200Hz. Each point in the above figure represents the average signal taken from the center of a field of cells between the electrodes.

Huang, C.J. *et al.* NATURE BIOTECHNOLOGY **24,** 439-446, (2006).